REMARKS

1. Status of the claims

Claims 1-24, as filed, are pending. Applicants acknowledge that claims 9, 10, 18 and 19 are currently under examination, and that all other claims are formally withdrawn from consideration, in order to facilitate examination. However, Applicants wish to retain their rejoinder rights to all claims capable of rejoinder, and elect to defer making any required amendments until such time as the pending claims are acknowledged to be patentable. Claim 9 is amended herein.

2. The claims as amended fulfill the requirements of 35 U.S.C. § 112, 1st ¶.

The pending claims maintains the rejection under 35 U.S.C. §112, first paragraph for failing to fulfill the written description requirement for the claim elements "melatonin agonists" and "compounds that increase endogenous melatonin production." The Action relies substantially on the rubrics set forth in the Written Description Guidelines as promulgated by the Patent and Trademark Office on January 6, 2001, as well as Federal Circuit decisions including *University of Rochester v. G.D. Searle*. Applicants respectfully traverse.

Applicants understand that their previous arguments were not persuasive, and that at least part of the reason for this outcome are that they did not completely draw the Office's attention to the distinctions between their claims and with the principles recited in the Action. To be clear, one important distinction is that in the *Rochester* case, the inventors had discovered the biological target (COX-2) but claimed a method for differential inhibition of COX-2 (and not COX-1) while providing no disclosure of any compound having the differential inhibition property. Moreover, since no one in the art was aware of the existence of COX-2 before the inventors' discovery, no one had attempted to find such a differentially-inhibiting compound. Further, existing compounds selected for analgesia were known to not have significant differential inhibiting properties (i.e., they inhibited both COX-1 and COX-2 with clinically insignificant differences). Thus, the Court in *Rochester* properly determined that a method claim requiring the use of an undisclosed compound failed to satisfy the written description requirement.

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Applicants' claims are completely different. Unlike the case in *Rochester*, the art recognized several species of melatonin antagonists and compounds that increase endogenous melatonin production. Applicants' submission of art showing this knowledge was intended to be illustrative, not exhaustive. Recognizing that the Office requires more of a showing of the extent of the knowledge in the art, Applicants respectfully bring the following art references to the Office's attention, relating to compounds that increase endogenous melatonin production:

Arai, Y. C., W. Ueda, et al. (2004). "Isoflurane increases, but sevoflurane decreases blood concentrations of melatonin in women." Journal of Anesthesiology **18**(3): 228-231.

Demisch, K., L. Demisch, et al. (1986). "Melatonin and cortisol increase after fluvoxamine [letter]." British Journal of Clinical Pharmacology **22**(5): 620-622.

Désir, D., C. Kirkpatrick, et al. (1983). "Ritodrine increases plasma melatonin in women." Lancet **1**(8317): 184-185.

Garde, E., S. Micic, et al. (1994). "8-methoxypsoralen increases daytime plasma melatonin levels in humans through inhibition of metabolism." Photochemistry and Photobiology **60**(5): 475-480.

Grota, L. J., A. J. Lewy, et al. (1985). "Psoralen increases melatonin levels without ultraviolet light." Annals of the New York Academy of Sciences **453**: 385-387.

Oxenkrug, G. F., I. M. McIntyre, et al. (1986). "Single dose of tranylcypromine increases human plasma melatonin." Biological Psychiatry **21**: 1081-1085.

Palazidou, E., A. Papadopoulos, et al. (1992). "Noradrenaline uptake inhibition increases melatonin secretion, a measure of noradrenergic neurotransmission, in depressed patients." Psychological Medicine **22**(2): 309-15.

Souêtre, E., E. Salvati, et al. (1987). "5-Methoxypsoralen increases the plasma melatonin levels in humans." Journal of Investigative Dermatology **89**(2): 152-155.

Applicants also submit the following references relating to melatonin agonists:

Davies, D.J. et al. (1998). "Mapping the Melatonin Receptor. 5. Melatonin Agonists and Antagonists Derived from Tetrahydrocyclopent[b]indoles, Tetrahydrocarbazoles and Hexahydro cyclopent[b]indoles." Journal of Medicinal Chemistry **41**(4): 451-467.

Garratt P.J. et al. (1995). "Mapping the Melatonin Receptor. 3. Design and Synthesis of Melatonin Agonists and Antagonists Derived from 2-phenyltryptamines." Journal of Medicinal Chemistry **38**(7): 1132-1139.

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Le Gouic S. et al. (1996). "Effects of both a melatonin agonist and antagonist on seasonal changes in body mass and energy intake of the garden dormouse." International Journal of Obesity **20**(7): 661-667.

Mathé-Allainmat, M. et al. (1996). "Synthesis of 2-amido-2,3-dihydro-1H-phenelene derivatives as new conformationally restricted ligands for melatonin receptors." Journal of Medicinal Chemistry **39**(16): 3089-3095.

Spasoni, G. et al. (1993). "2-Substituted 5-methoxy-Nacyltryptamines: synthesis, binding affinity for the melatonin receptor, and evaluation of the biological activity." Journal of Medicinal Chemistry **36**(25): 4069-4074.

Tarzia G. at al. (2000). "Design and synthesis of melatonin receptor agonists and antagonists. Farmaco **55**(3): 184-187.

Tarzia G. et al. (1997). "1-(2-Alkaneamidoethyl)-6-methoxyindole deriviatives: A new class of potent indole melatonin analogues. Evaluation of the biological activity." Journal of Medicinal Chemistry **40**(13): 2003-2010.

All of these references are submitted herewith in an Information Disclosure Statement.

These references supplement the references already of record, including:

Kräuchi et al. (1995). "Evidence for a phase advance in circadian temperature regulation after acute melatonin and a melatonin agonist (S-20098)." Sleep Research **24**: 526.

Martinet et al. (1996). "Entrainment of circadian rhythms by S-20098, a melatonin agonist, is dose and plasma concentration dependent." Pharmacology Biochemistry and Behavior 54: 713-718.

Redman et al. (1995). "Dose dependent effects of S-20098, a melatonin agonist, on direction of re-entrainment of rat circadian activity rhythms." Psychopharmacology (Berl) 118(4): 385-90.

Sack, R. L. and A. J. Lewy (1986). "Desmethylimipramine treatment increases melatonin production in humans." Biological Psychiatry **21**: 406-410.

And of course there has been additional disclosure up until the filing date of the instant application.

The point is that unlike the *Rochester* situation, here the skilled worker had a veritable armamentarium of molecules known to be melatonin agonists or to increase endogenous

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melatonin production. This is in direct contrast to the *Rochester* situation and distinguishes this case from that one. It is not and cannot be the rule that an applicant is forced to recite every species in a generic class of compounds, or patents would be nothing more than lists of such species. Any such requirement, or application of the written description requirement of 35 U.S.C. §112, first paragraph, would be contrary to established law. "[A] patent need not teach, and preferably omits, what is well known in the art." (*MPEP* § 2163(II)(A)(2)); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed.Cir.1986). Applicants respectfully submit that there is no basis for the current written description requirement, in view of the status of the knowledge in the art and the proper application of settled law.

Applicants thus respectfully contend that the evidence of record supports their position that the claims fulfill the written description requirement, and request that the Examiner withdraw this ground of rejection

Applicant believes that all grounds of rejection on 35 U.S.C. §112, first paragraph grounds have been traversed by argument and overcome by the evidence submitted herewith, and respectfully ask the Examiner to withdraw the rejections asserted on this basis.

3. <u>The claims as amended are not anticipated by the cited art.</u>

The pending claims stand rejected as anticipated under 35 U.S.C §102(b) in view of the teachings of International Patent Application Publication No. WO 95/05819; "the Lewy PCT application"). Applicants respectfully traverse this ground of rejection.

As noted in response to the prior Office Action, to anticipate the pending claims the cited reference must teach each and every limitation of the claimed invention. That is not the case here. Pending claim 9, as amended recites:

> 9. (Currently amended) A method for achieving a circadian rhythm phase-delaying effect in a human, the method comprising the step of administering to the human an amount of melatonin, melatonin agonist or compound that increases endogenous production of melatonin in the human, wherein said administration produces in the human a plasma melatonin or agonist concentration of greater melatonin or equivalent agonist levels during the time interval from about CT 18 to about CT 6 than from the time interval from about CT 6 to about CT 18, <u>wherein plasma melatonin or equivalent agonist levels are elevated during a time interval beginning before and extending past the human's endogenous melatonin offset time</u>.

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Applicants request that the Office consider the amended claim with regard to the distinctions set forth herein to the teachings of the Lewy PCT application.

First, there is the timing of melatonin administration as taught by the Lewy PCT application as follows:

> The human melatonin PRC also indicates the presence of a time interval for each individual during which administration of exogenous melatonin results in clear and unequivocal phase-delay responses. Within this interval, the time of administration of melatonin is related to the magnitude of the resulting phase delay shift of the PRC. The present invention directs the administration of melatonin . . . to achieve a phase delay between about CT 12 to about CT 6. The predicted phase advance or phase delay is more likely if the melatonin administration time occurs within these two intervals, respectively. (page 7, lines 13-20).

From this passage it can be seen that the Lewy PCT teaches a broader time interval for melatonin administration to achieve a phase delay (CT 12 to CT 6) than is taught and claimed by the instant application (CT 18 to CT 6). Moreover, the Lewy PCT does not teach that the time interval in which there are elevated physiological melatonin levels should extend past the human's endogenous melatonin offset time (CT 0). While the Lewy PCT focuses solely on administration times, the instant application recognizes for the first time that administration time is an incomplete measure of how to achieve an optimum phase delay. As taught in the instant application, the combination of administration time and exogenous melatonin pulse duration (which depends on whether melatonin is administered as an immediate release, sustained release or delayed release formulation, or appropriate combinations thereof) must be chosen so that exogenous melatonin administration causes increased physiological melatonin levels that extend past the melatonin offset time at CT0.

Similarly, the Lewy PCT teaches:

> The human melatonin PRC described in U. S. Patent Serial No. 5,242,941 suggested that exogenous melatonin would be most effective when administered during the light period, to compete with light as a "substitute for darkness". The present invention is based on our further findings that *the critical variable* in determining the proper time for melatonin administration is *the relationship between the time of melatonin administration and the DLMO time of an individual human.* This finding has provided the basis for the methods of the instant invention, which methods enable treatment of a variety of circadian rhythm phase disturbances in

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humans by administration of exogenous melatonin at the times described hereinbelow. (p. 5, l. 11-20)

Thus, it can be seen that by being focused on administration times, the Lewy PCT was limited to when elevated physiological melatonin concentrations began to rise and contained no teachings about when the elevated physiological melatonin concentrations fell to normal levels. In contrast, the instant application teaches that what is also important is the time when elevated physiological melatonin levels begin to fall, and that for phase delays this time must be later than the endogenous melatonin offset time (i.e., after CT0).

Finally, the pending claims have been amended to more explicitly recite the feature that, for a phase delay, the period of elevated plasma melatonin *etc.* concentration extends past the endogenous melatonin offset time (CT 0). The Lewy PCT application teaches:

> The present inventors have discovered that the time of administration of exogenous melatonin relative to the time of endogenous melatonin *onset* is critical to the production of the appropriate phase-shifting effect. The time of exogenous melatonin administration is kept constant relative to the human's DLMO time, which changes during a course of exogenous melatonin treatment as provided by the methods of the invention. Thus, the actual clock-time of melatonin administration also changes (p. 6, l. 23-29).

> The human melatonin PRC also indicates the presence of a time interval for each individual during which administration of exogenous melatonin results in clear and unequivocal phase-delay responses. Within this interval, the time of administration of melatonin is related to the magnitude of the resulting phase delay shift of the PRC. The present invention directs the administration of melatonin to achieve . . . to achieve a phase delay between about CT 12 to about CT 6. (p. 7, l. 13-20).

Thus, while the Lewy PCT application teaches melatonin administration times between CT 12 and CT 6, there is no teaching that the period of elevated physiological melatonin concentration should extend past the endogenous melatonin offset (i.e., CT 0), nor any teaching to have higher melatonin concentration during one part of the PRC (i.e., the twelve-hour interval from CT18 to CT6). Indeed, in the absence of this teaching the maximum dose disclosed in the Lewy PCT (0.5mg melatonin; see page 6, lines 6-8) would produce elevated physiological melatonin levels for no more than 5 hours, meaning an immediate release dosage form could not be administered before about CT19; if administered before CT19 physiological levels of melatonin would fall

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prior to the time of endogenous melatonin offset (CT0). This is not taught in the Lewy PCT. In addition, six hours of the melatonin administration interval (CT0 to CT6) of the interval (CT 12 to CT 6) taught by the Lewy PCT for producing phase delays would not extend past the endogenous melatonin offset time (CT0) and thus not produce the maximum phase delay taught in the present application.

The Lewy PCT application has no teaching of maintaining elevated plasma melatonin levels to extend past a human's endogenous melatonin offset time (CT 0) to effect a phase delay in the human phase response curve, nor any teaching that the plasma melatonin concentration should be higher over the interval from CT 18 to CT 6 than in the interval from CT 6 to CT 18. Indeed, in view of the limited melatonin dosage amounts taught in the Lewy PCT application, it is likely that overall the integrated levels of melatonin (endogenous and exogenous) in the time periods of CT 6 and CT 18 are greater than in the interval from CT 18 to CT 6. There is no teaching that this is not a circumstance consistent with inducing a phase delay in a human.

The teachings of the Lewy PCT application is limited and focused on the administration time of melatonin etc. and its relationship to an individual's DLMO (so much so that the Lewy PCT application contains teachings for an individual to determine DLMO). The instant application discloses for the first time the concept that it is the extent of the exogenous melatonergic pulse that is useful for producing a circadian rhythm phase shift. As taught by the inventors in the instant application, the pharmacokinetics of the increased melatonin levels due to exogenous melatonin or a compound that increases endogenous melatonin (as illustrated in the references set forth above) or to melatonin agonist levels optimally are elevated at a time that begins before and extends past the endogenous melatonin offset time (CT0) to produce a phase delay. In contrast to the teachings of the Lewy PCT application, the present invention teaches that it is the duration of the period of greater than quiescent melatonin levels and elevated physiological melatonin concentrations extending past the time of endogenous melatonin offset (i.e., CT 0) to achieve an optimal phase delay. The Lewy PCT application taught that phase delays were optimally produced by administering melatonin between CT 12 and CT 2, but at the doses taught there was little likelihood that the period of elevated melatonin *etc.* would extend past the endogenous melatonin offset time (CT 0), and no teaching that this was desirable. Moreover, the Lewy PCT application taught that phase delays could be *most effectively* produced

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by exogenous melatonin administration *after* CT 0, which is inconsistent with the teachings of the instant application and contrary to the express limitations of the claims as amended. Indeed, in view of the lower doses of melatonin taught in the Lewy PCT application, following the teachings of the Lewy PCT would not ensure that the overall integrated levels of melatonin (endogenous and exogenous) in the time periods of CT 6 and CT 18 would not be greater than in the interval from CT 18 to CT 6. There was no explicit teaching that higher doses of exogenous melatonin administered during the phase advance interval (CT 6 to CT 18) could cause less of a phase delay. Applicants respectfully remind the Office that these are method claims, and so the specific recitations for melatonin *etc.* administration times are relevant to the distinctions Applicants raise in these remarks.

Finally, Applicants note that the U.S. Patent and Trademark Office has determined that claims directed to phase advance aspects of this invention have been granted as U.S. Patent No. 6,638,936; for the Examiner's convenience these claims are set forth in Exhibit A submitted herewith. The Lewy PCT was of record in the parent application. Applicants respectfully contend that the asserted ground of rejection is inconsistent with this prior determination of patentability, and further respectfully contend that this is yet another reason to withdraw rejection on 35 U.S.C. §102(b) grounds.

Applicants respectfully contend that, contrary to the assertions in the action that the claimed invention is anticipated by either their own prior patent application, the claimed invention sets forth a new method for administering melatonin etc. to a human suffering from jet lag, and thus is not anticipated by these references. Applicants respectfully request that the Examiner withdraw this ground of rejection.

4. The claims are not barred under the judicially-created doctrine of obviousness-type double patenting.

The pending claims stand rejected under the judicially-created doctrine of obviousness-type double patenting over a variety of Applicants' earlier U.S. patents. Applicants respectfully contend that their own prior art does not render their claims obvious, and wish to bring to the Office's attention the relevant relationships between this application and the other applications set forth in the rejection.

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The Action sets forth the following prior patents: 5,242,941, 5,420,152, 5,591,768, 5,716,978, 6,638,963 and 6,794,407. Applicants point out that their specification was amended upon filing to recite the following relationships between these applications:

This application is a divisional of U.S. patent application Serial No. 08/840,382, filed April 29, 1997, which is a continuation-in-part of U.S. Serial No. 08/778,842, filed January 6, 1997, now U.S. Patent No. 6,069,164, issued May 30, 2000, and also a continuation-in-part of U.S. Serial No. 08/779,797, filed January 7, 1997, now abandoned.

Applicants note that USSN 08/840,382 is now U.S. Patent No. 6,638,963 and hence that the Office, having determined during prosecution of this prior patent that the claims of the instant application are patentably distinct, cannot impose now require submission of a terminal disclaimer in contradiction of its earlier determination. 35 U.S.C. §121; *Pfizer, Inc. v. Teva Pharma. Inc.*, Docket No. 2007-1271 (March 7, 2008).

The Action admits that the Office used the claims of the '963 patent as a "representative rejection," and Applicants respectfully submit that this was improper in view of the Office's separate patentability determination. Applicants further submit that the other patents recited as falling within the scope of the obviousness-type double patenting rejection are subject to the same distinctions Applicants set forth above with regard to the Lewy PCT application. For those reasons, Applicants respectfully ask the Office to reconsider these rejections under the appropriate examination standard, and that the Office determine that the pending claims are patentably distinct from the claims of each and every one of those patents, at least for the reasons set forth herein.

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CONCLUSIONS

Applicant believes that all grounds of rejection have been overcome by amendment or traversed by argument, and request that the pending claims be passed to issue.

If the Examiner in charge of this application believes it to be helpful at any time during prosecution of this application, she is invited to contact Applicants' undersigned representative by telephone at (312) 913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff LLP

Date: June 4, 2008

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EXHIBIT A: U.S. PATENT NO. 6,638,963 CLAIMS

1. A method for achieving a circadian rhythm phase-shifting effect in a human, the method comprising the step of administering to the human an amount of melatonin, melatonin agonist or compound that increases endogenous production of melatonin in the human, wherein said administration produces in the human a plasma melatonin or agonist concentration of greater than quiescent melatonin or equivalent agonist levels at a time that overlaps with either onset of endogenous melatonin production in the human or offset of endogenous melatonin production in the human, wherein when the circadian rhythm phase-shifting effect is a phase advance, melatonin, melatonin agonist or compound that increases endogenous production of melatonin in the human is administered at a time after about CT 6 and prior to CT 14 to produce plasma melatonin or agonist concentrations of greater than quiescent melatonin or equivalent agonist levels that overlap endogenous melatonin production onset, said greater than quiescent melatonin or equivalent agonist levels rise before the melatonin onset and fall after the melatonin onset; or wherein when the circadian rhythm phase-shifting effect is a phase delay, melatonin, melatonin agonist or compound that increases endogenous production of melatonin in the human is administered at a time after about CT 18 and prior to CT 1 to produce plasma melatonin or agonist concentration of greater than quiescent melatonin or equivalent agonist levels that overlaps offset of endogenous melatonin production, said greater than quiescent melatonin or equivalent agonist levels rise before the melatonin offset and fall after the melatonin offset.

2. A method according to claim 1 wherein the circadian rhythm phase-shifting effect is a phase advance and wherein administration of melatonin, melatonin agonist or a compound that increases endogenous melatonin production in the human produces in the human a plasma melatonin or agonist concentration of greater than quiescent melatonin or equivalent agonist levels after CT 6, that persists until at least after CT 14 and is reduced to quiescent melatonin or equivalent agonist levels between about CT 18 and the offset of endogenous melatonin production.

3. A method according to claim 1 or 2 wherein exogenous melatonin, melatonin agonist or compound that increases endogenous production of melatonin in the human is administered to a human in an immediate-release formulation.

4. A method according to claim 1 or 2 wherein exogenous melatonin, melatonin agonist or compound that increases endogenous production of melatonin in the human is administered to a human in a delayed-release formulation.

5. A method according to claim 1 or 2 wherein exogenous melatonin, melatonin agonist or compound that increases endogenous production of melatonin in the human is administered to a human in a sustained-release formulation.

6. A method according to claim 2 wherein exogenous melatonin, melatonin agonist or compound that increases endogenous production of melatonin in the human is administered to a human formulation in any combination of an immediate-release formulation, a delayed-release formulation or a sustained-release formulation.

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7. A method for achieving a circadian rhythm phase-shifting effect in a human, the method comprising administering to the human an amount of melatonin, melatonin agonist or compound that increases endogenous production of melatonin in the human, wherein said administration produces in the human a plasma melatonin or agonist concentration of greater than quiescent melatonin or equivalent agonist levels for a time or in a concentration that is different during a time interval from about CT 6 to about CT 18 than that produced during the time interval from about CT 18 to about CT 6, wherein when the circadian rhythm phase-shifting effect is a phase advance, melatonin, melatonin agonist or compound that increases endogenous production of melatonin in the human is administered after about CT 6 and prior to CT 14, or when the circadian rhythm phase-shifting effect is a phase delay, melatonin, melatonin agonist or compound that increases endogenous production of melatonin in the human is administered after about CT 18 and prior to CT 1.

8. A method according to claim 7 wherein the circadian rhythm phase-shifting effect is a phase advance, the method comprising administering to the human an amount of melatonin, melatonin agonist or compound that increases endogenous production of melatonin in the human, wherein said administration produces in the human a plasma melatonin or agonist concentration of greater than quiescent melatonin or equivalent agonist levels for a time or in a concentration during a time interval from about CT 6 to about CT 18 that is greater than that produced during the time interval from about CT 18 to about CT 6, wherein melatonin, melatonin agonist or compound that increases endogenous production of melatonin in the human is administered after about CT 6 and prior to CT 14.

9. A method for alleviating a circadian rhythm disorder in a human, the method comprising the step of achieving a circadian phase-shifting effect in the human according to the method of claim 1.

10. The method of claim 9 wherein the circadian rhythm disorder is jet lag.

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